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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/448,378	11/23/1999	KENNETH BRASEL	2836-US-DIV	4973

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EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	PAPER NUMBER
1644	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/448,378	BRASEL ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6,7,20,22-24,28,30-35 and 40-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6, 7, 20, 22-24, 28, 30-35 and 40-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

Applicant's submission, filed on 02/28/2007, has been entered.

Applicant's amendment, filed 02/28/2007, has been entered.
Claims 6 and 20 have been amended.

Claims 1-5, 8-19, 21, 25-27, 29, 36-39 and 54-56 have been canceled previously.

Claims 6, 7, 20, 22-24, 28, 30-35 and 40-53 are pending.
Applicant's election without traverse of Group I and the species GM-CSF has been ackno

2. This Action will be in response to applicant's amendment, filed 02/28/2007.
The rejections of record can be found in the previous Office Actions.

3. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-10 and 12-17 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed.
The specification as originally filed does not provide support for the invention as now claimed: "for a duration of time".

Applicant's argument, filed 02/28/2007, does not appear to direct support to the newly added claim recitation of "for a duration of time".

Upon a review of the instant specification, the term "duration" or the phrase "duration of time" does not appear to be described.
It appears that applicant is relying, at least in part, upon the disclosure of the Examples provided in the specification as filed.

While the instant specification as filed describes "administering Flt3-ligand prior to, concurrently or with or subsequent to administration of an antigen to a patient for immunization purposes" (e.g., see page 10, paragraph 1 of the instant specification) as well as "typical dosing of Flt3-ligand in the ranges from about 10 µg per square meter to about 1000 µg per square meter" (e.g., see pages 12-13, overlapping paragraph of the instant specification);

The phrase "duration of time" is not described nor defined.

The ordinary artisan would not be apprised of the metes and bounds or scope of the period of time" during which something exists or lasts".

See the Definition of "duration" on page 411 of Webster's II New Riverside University Dictionary, The Riverside Publishing Company, Boston, MA, 1994.

Applicant has not pointed out sufficient description in the specification as filed as to the term "duration" or the phrase "duration of time" in the specification as filed, as currently claimed.

Rather, it appears that applicant has relied upon the general terms and disclosure of dosing and modes of administration of Flt3-ligand and the use of an experimental model to set forth a new "limitation" without a clear definition as to the metes and bounds or scope of "duration of time".

The instant claims now recite limitations which were not clearly disclosed in the priority applications as well as the specification as-filed, and would have changed the scope of the priority applications and do change the scope of the instant disclosure as-filed.

It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

The specification as filed does not provide a sufficient written description of the newly added "duration of time". The specification does not provide sufficient blaze marks nor direction for the instant methods encompassing the above-mentioned "duration of time", as currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office Action.

Alternatively, applicant is invited to provide sufficient written support for the "limitation" indicated above.

See MPEP 714.02 and 2163.06

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims rejected under 35 U.S.C. § 103(a) as being unpatentable over Lyman et al. (WO /94/28391; 1449) in view of Elliott et al. (U.S. Patent No. 5,478,556), Srivastava et al. (U.S. Patent No. 6,017,544) and Brem et al. (U.S. Patent No. 5,626,862) essentially for the reasons set forth in the previous Office Actions.

Applicant's arguments, filed 02/28/2007, in conjunction with a study carried out in mice have been fully considered but are not found convincing essentially for the reasons of record.

Applicant's arguments and the examiner's rebuttal are essentially the same of record.

Again, applicant asserts that the examiner fails to consider that none of the references teach or suggest alone or in combination the use of Flt3-ligand in an amount sufficient to an increase in the number of dendritic cells as claimed.

Again, applicant distinguishes the amount of time that Lyman expanded hemopoietic cells in cultures with Flt3-ligand with the amount of time relied upon in the instant Examples with respect to both in vitro culture conditions associated with generating large number of dendritic cells in vitro or in vivo.

Applicant argues that the hemopoietic stem / progenitor cells must be exposed to Flt3-ligand for an extended period of time to generate an increase in the number of dendritic cells in a patient.

In focusing on the recitation of "a sufficient amount" and "a sufficient duration of time", applicant asserts that there is no motivation in the art to achieve the claimed invention, such as augmenting the tumor-specific immune response by increasing the number of dendritic cells.

In turn, applicant submits that the lack of motivation renders the claims unobvious whether or not there are unexpected results.

Further, applicant, in combination with various legal decisions, asserts that the combination of Flt3-ligand and GM-CSF administered in combination with a particular antigen (BLP25) provided unexpectedly superior results in terms of preventing formation of tumors.

As pointed out previously, applicant's basis for this assertion of unexpected results appears to be based upon one particular experimental model study.

It is noted that point #4 of the Conclusions of the Study are that the results look encouraging and it would be worthwhile to repeat and extend this experiment.

Similar statements are made at the end of the Discussion of the study.

Also, it is noted that the Discussion of the Study indicates that lipid A rapidly enhances dendritic cell maturation.

Therefore, applicant is relying upon a single experimental study as well as the contribution of lipid A in the study to assert unexpected results of the combination of FLT3-ligand and GM-CSF, as broadly claimed.

While applicant relies upon an extended period of time to generate an increase in the number of dendritic cells in a patient, the specification as filed does not appear to define "the amount sufficient to generate an increase in the number of patient's dendritic cells".

Giving the claims the broadest reasonable interpretation, see In re Zletz, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989) (during ex parte prosecution, claims are to be given their broadest reasonable interpretation consistent with the description of the invention in the specification),

the claims read on methods of administering Flt3-ligand in "effective amounts" and "duration of time" that generates an increase in the number of the patient's dendritic cells.

The claims do not specify any particular level of "amount" or duration".

Therefore, the claims read on any measurable increase in the number of the patient's dendritic cells that augment tumor-specific immune responses in a patient.

Thus, all that is required is that the prior art methods elicit any measurable level of augmenting tumor-specifc immune response by increasing the number of dendritic cells.

Any increase or mobilization of a patient's dendritic cells via the administration of Flt3-ligand would meet the sufficient or effective amounts of Flt3-ligand to meet the claim (e.g. see page 10, paragraph 1 of the instant specification).

The typical dosages of Flt3-ligand ranging from about 10 – about 1000 µg per square meter indicated on pages 12-13, overlapping paragraph of the instant specification are the same exact dosages described by page 26, paragraph 1 of Lyman et al. (WO 94/28391).

Both disclosures provide for the same determination and scaling of dosing to provide for effective amounts of Flt3-ligand alone or in combination with other active materials.

Lyman et al. also provides for the administration of Flt3-ligand alone, sequentially or in concurrent combination with other cytokines listed therein, including GM-CSF as well as simultaneously or subsequent to the infusion of cells in patients (see Example 13, particularly page 43, paragraph 1).

It is noted that Lyman et al. teach that such procedures are useful for the expansion of hemopoietic cells as well as the ability to elevate a patient's immune response (see Background of the Invention and the Summary of the Invention on pages 1-6 of the Lyman et al.).

Although applicant focuses on "the amount sufficient for a sufficient duration to generate an increase in the number of patient's dendritic cells",

applicant has not sufficiently distinguished the dosing and modes of administration that appear to be the same or nearly the same as encompassed by the instant claims and as disclosed in the specification as filed.

"Expected beneficial results are evidence of obviousness of a claimed invention, just as unexpected results are evidence of unobviousness thereof." In re Gershon, 372 F.2d 535, 538, 152 USPQ 602, 604 (CCPA 1967).

See MPEP 716.02(c).

Also, see KSR International v. Teleflex Inc., U.S. Supreme Court No. 04-1350 (April 30, 2007) for guidance as to the determination of obviousness.

Here, the prior art clearly provides for providing GM-CSF can lead to the elimination of tumor cells in a patient in a potent and specific manner and this is done in combination with other chemotherapeutic agents such as cytokines, which can have broad immunoregulatory properties (e.g. see Brem et al., Combinations with other biologically active compounds on columns 8-9).

In addition, the prior art recognized the advantages of providing stimulation to various compartments of the recipient to maximize the physiological and therapeutic response (e.g. see Background of the Invention of Elliott et al. and Formulation and

Administration of the Complexes on columns 11-12 of Srivastava as well as the citation of Brem et al. herein).

The prior art as indicated previously and herein provide for combining various bioactive agents, including cytokines, including GM-CSF in combination with other cytokines, including multiple or subsequent administration of said bioactive substances / cytokines to maximize physiological and therapeutic responses (e.g., see columns 11-12 of Elliott et al.; columns 8-9 of Brem et al.; and columns 1-12 of Srivastava et al.).

In addition, all of the references are consistent with the instant specification that dosages and modes of administration depend on variables known and practiced in the art at the time the invention was made.

Also, as indicated previously and provide herein, the prior art clearly provides for the use of cytokines such as GM-CSF to expand the numbers and augment the activity of dendritic cells in generating tumor-specific immune responses.

For example, the prior art clearly provides for providing GM-CSF can lead to the elimination of tumor cells in a patient in a potent and specific manner and this is done in combination with other chemotherapeutic agents such as cytokines which can have broad immunoregulatory properties (e.g. see Brem et al., Combinations with other biologically active compounds on columns 8-9).

Therefore, the prior art recognized the advantages of providing stimulation to various compartments of the recipient to maximize the physiological and therapeutic responses and that such advantages could be accomplished with cytokines, such as Flt3-ligand and GM-CSF and combinations with cytokines thereof, that enhance the growth and /or elaboration of hemopoietic or immune-type cells in cancer patients.

The effective amounts provide by the prior art either with respect to Flt3-ligand, GM-CSF or combinations of cytokines are consistent with that encompassed by the broadest reasonable interpretation of the claimed methods. Similarly to applicant's assertions, the prior art provides for multiple administration of effective amounts of cytokines as well as known practices by the ordinary artisan to achieve the therapeutic effects of stimulating hemopoietic cells, including dendritic cells, in achieving anti-tumor immune responses in cancer patients at the time the invention was made and that combinations of such cytokines were expected to maximize such desired endpoints.

Applicant's reliance upon combining cytokines to increase responses is consistent with the same or similar teachings of the prior art. Hemopoietic and immune-type cells, including stem / progenitor cells, express multiple receptors for growth factors and that

interactions with one or more of these receptors via the growth factors influence the growth and development of the cells. Consistent with the prior art teachings of combining cytokines to maximize response, it has been long appreciated by the ordinary artisan that combinations of growth-promoting agents or factors were necessary to elicit / maximize desired responses by hemopoieitic / immune-type cells.

Applicant's reliance upon combining cytokines such as Flt3-ligand and GM-CSF to increase responses when compared to each cytokine acting alone is consistent with the prior art teachings that maximizing physiological and therapeutic responses was expected to be achieved by combinations of cytokines.

The strongest rationale for combining references is a recognition in the art that some advantage or expected beneficial result would have been produced by their combination. This recognition may be an expressed statement in a reference, an implication that can be drawn from one or more references or a convincing line or reasoning based upon established principles or legal precedent.

One of ordinary skill in the art at the time the invention was made would have been motivated to select a combination of cytokines, including Flt3-L and GM-CSF in combination with tumor antigens to treat human cancer; given the properties of said cytokines to augment immune responses including augmenting immune responses to cancer antigens and to stimulate hemopoietic cells to alleviate the effects of chemotherapy and radiation therapy in cancer patients.

While Lyman et al. may differ from the claimed methods by not disclosing the known administration of a tumor antigen to a cancer patient to induce an immune response to the desired tumor antigen and that the administration of Flt3-L and/or GM-CSF would lead to an increase in the number of dendritic cells per se.

Lyman et al. teach the administration of sufficient / effective amounts of Flt3-L to cancer patients that are consistent with instant disclosure and broadest reasonable interpretation of the claims.

In contrast to applicant's assertions, the prior art clearly provides for generating tumor-specific immune responses that include, in part, the increase in the number of the patient's dendritic cells as well as the increase of anti-tumor responses in said patients.

Again, applicant is reminded that the reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. In re Linter, 173 USPQ

560 (CCPA 1972) (discussed below); In re Dillon , 16 USPQ2d 1897 (Fed. Cir. 1990), cert. denied , 500 U.S. 904 (1991) (discussed below).

Although Ex parte Levengood, 28 USPQ2d 1300, 1302 (Bd. Pat. App. & Inter. 1993) states that obviousness cannot be established by combining references "without also providing evidence of the motivating force which would impel one skilled in the art to do what the patent applicant has done " (emphasis added), reading the quotation in context it is clear that while there must be motivation to make the claimed invention, there is no requirement that the prior art provide the same reason as the applicant to make the claimed invention.

Therefore, the reason or motivation to combine may often suggest doing what the inventor has done, but for a different purpose or to solve a different problem than that asserted by the inventor. See MPEP 2144.

Therefore the rejection of record is maintained for the reasons of record and addressed above and reiterated for applicant's convenience.

The instant claims are drawn to methods of augmenting immune responses in cancer patients with FLT3-ligand and GM-CSF.

Lyman et al. teach methods of treating cancer patients by administering FLT3-L in combination with other cytokines, including GM-CSF including treating intestinal damage resulting from irradiation and chemotherapy and stimulating immune responses as well as hemopoietic cells to improve the quality of life of a patient (see entire document; Background of the Invention; Summary of the Invention, including Claims). Lyman et al. teach the FLT3-L and its recombinant forms and sequences encompassed by the claimed invention (See Detailed Description of the Invention and Examples).

Lyman et al. differs from the claimed methods by not disclosing the known administration of a tumor antigen to a cancer patient to induce an immune response to the desired tumor antigen and that the administration of FLT3-L and/or GM-CSF would lead to an increase in the number of dendritic cells per se.

Both Elliott et al. and Srivastava teach that GM-CSF teach the known administration of GM-CSF with tumor antigens to simulate the immune system.

Elliott et al. teach the vaccination of cancer patients with tumor associated antigens mixed with cytokines, including GM-CSF, including the stimulation of antigen-processing (see entire document, Background of the Invention, Summary of the Invention, Detailed Description of the Invention). Both the tumor associated antigens and the GM-CSF can be administered at various times (see Summary of the Invention).

Srivastava teach methods of augmenting cancer vaccines with cytokines including GM-CSF (see entire document; including Summary of the Invention, including column 4, paragraph 6; Detailed Description, including column 12, paragraph 3; Claims.). Srivastava teach compositions comprising cancer cells as well as cancer antigens serve as sources for immunization against tumor antigens of interest (See entire document, including Background of the Invention, Summary of the Invention and Detailed Description of the Invention). In addition to combining cancer therapies, including surgery, radiation therapy and chemotherapy (columns 5-6, overlapping paragraph), dosages and modes of administration depend on variables known and practiced in the art at the time the invention was made (e.g. see columns 11-12, Formulation and Administration of the Complexes). Srivastava teach that a number of tumor types, including fibrosarcoma, can be treated (see column 6, paragraphs 4-5).

Brem et al. teach the GM-CSF is a cytokine that systematically activate cytotoxic T lymphocytes which have shown to lead to the elimination of tumor cells in a potent and specific manner, by stimulating the growth and activity of several myeloid cells and playing a critical role in the migration and development of professional antigen presenting cells such as dendritic cells (see column 8, paragraph 2).

Given the teachings of combining FLT3-L and GM-CSF to treat cancer by Lyman et al. in combination with the teachings of Elliott et al. and Srivastava et al. that GM-CSF was potent in cancer vaccination, one of ordinary skill in the art would have combined FLT3-L, GM-CSF and tumor antigens to stimulate the hemopoietic and immune system of cancer patients, including the vaccination to tumor associated antigens. Given the teachings of stimulating the hemopoietic and immune systems with FLT3-L and GM-CSF with the teachings of administering tumor antigens to activate immune responses and antigen presentation, one of ordinary skill in the art would have had an expectation of success that the administration of FLT3-L and GM-CSF would increase the number of dendritic, as evidenced by the teachings of Brem et al. that GM-CSF activates immune responses via dendritic cells.

Given the teachings of the prior art to treat and augment immune responses in cancer patients and that the administration of cytokines and tumor antigens were based on variables and procedures known and practiced by the ordinary artisan, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer tumor antigen at various times with respect to cytokine administration, including the administration of tumor antigen prior, concurrently and after cytokine administration.

One of ordinary skill in the art at the time the invention was made would have been motivated to select a combination of cytokines, including FLT3-L and GM-CSF in combination with tumor antigens to treat human cancer; given the properties of said

cytokines to augment immune responses including augmenting immune responses to cancer antigens and to stimulate hemopoietic cells to alleviate the effects of chemotherapy and radiation therapy in cancer patients.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments have not been found persuasive.

Here, the prior art provides sufficient motivation and expectation of success in arriving at the same manipulative steps as the claimed invention in treating patients having cancerous or neoplastic disease.

7. No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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